Chemotherapeutics in the therapy of influenza and other viral respiratory infections in children

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During different epidemic seasons, we conducted clinical and laboratory observations to study the therapeutic efficacy of rimantidine and arbidol in children with influenza and mixed viral infections, under both inpatient and outpatient settings. In the rimantidine trial, 742 school aged children and 60 children aged 3-6 years were observed who had been diagnosed with influenza type A, type B, types A and B, influenza in conjunction with other viral illness, or acute viral respiratory illness of non-influenza etiology. 402 children received rimantidine, and 400 received a placebo. The drug was given at a dose of 1.5 mg/kg body weight, 3 times a day for 3 days. In the arbidol trial, 158 children ages 1-14 years, with the diagnoses influenza type A, influenza in conjunction with other viral illness, or acute viral respiratory illness of non-influenza etiology were observed. Arbidol was administered at a dose of 10mg/kg body weight per day, given in 4 doses per day, for 5 days. Both drugs proved to be therapeutically effective in all influenza and acute viral respiratory illness types, particularly when the drugs were administered at the early stages of illness. With the drugs, the duration of fever, other symptoms of toxicity, and the amount of viral isolation were reduced. The medications did not produce adverse effects in the children, nor did they inhibit cell-mediated or humoral immunity, or the production of antiviral antibodies. The dynamics of markers for cellular immunity and macrophages confirmed the existence of immunostimulating activity in arbidol.

Influenza and other acute viral respiratory infections (AVRI) – in their social significance, a huge detriment to a population's health and a nation's economics – at present are in first place among all human diseases [1]. Even during the non-peak epidemic season, influenza and AVRI account for up to 40 % of all illnesses registered in clinics in adults, and more than 60 % in children [2, 3]. In addition, there exists no specific guaranteed vaccine against these diseases, and their treatment mostly consists of pathogenetic and symptomatic remedies; thus the arsenal of etiotropic antiviral drugs is not great.

In recent years in our country and abroad, a new direction has formed and continues to develop in the treatment of viral infections: chemotherapy. Of all the synthetic preparations active against the influenza virus, the one shown to have the most pronounced effect in experiments is rimantidine [4, 5]. Long-term studies on volunteers have established that this medication affects the reproductive process not only of Group A virus, but also RSV and para-influenza viruses [6]. The administration of rimantidine has protected both pregnant and newborn animals from falling ill with influenza

infections [7]. It has also been established that rimantidine, while not affecting Group B viral reproduction, protects animals from the viral toxicity which comes from toxogenic strains of Group B virus [8].

In recent years, the Chemical-Medicinal Drug Center of the Russian Scientific Research Chemical-Pharmaceutical Institute ("CMDC-RSRCPI") has seen the creation of the new chemical preparation "arbidol," which has a broad inhibiting action on early stage viral reproduction (influenza groups A and B, AVRI of non-influenza etiology, and herpes), immunomodulating activity, and interferon-potentiating properties.

When we began these studies, there already existed a significant amount of research detailing rimantidine and arbidol's safety and efficacy in influenza prophylaxis and treatment for adults. However, there was little data available on children. For this reason, we made our goal to research the safety and efficacy of rimantidine and arbidol against influenza in children.

Materials and Methods

The therapeutic efficacy of rimantidine was studied in controlled observations in separate epidemic seasons. The subjects were 742 school-aged children (554 in a hospital setting, 188 in a polyclinic) and 60 children younger than school age (3-6 years old). We used a commercial preparation which contained 50 mg active substance per tablet. The placebo was a tablet which had the same appearance and inactive ingredients as the rimantidine tablets (the control group). In all cases, the drug was first administered within the first 1-2 days of illness, and was given at a dose of 1.5 mg/kg body weight three times a day for three days.

The effectiveness of arbidol treatment was studied during the epidemic seasons 1994-95 and 1995-96, in 158 children (84 receiving arbidol and 74 receiving placebo). The children ranged in age from 1-14 years old, and had been diagnosed with influenza, or AVRI with influenza-like symptoms. The drug form for arbidol (0.025 g or 25 mg tablets) was developed and manufactured at CMDC-RSRCPI. The drug was given during the first days of illness, in the amount of 10 mg/kg body weight per day in 4 divided doses, for 5 days. At the same time, all the children received symptomatic remedies (cough syrup, nose drops, cups, plasters, multivitamins), and (when fever was present) fever-reducers.

In order to assure objective data on the treatment results of the compared groups (control vs. experimental), the studies included children with a moderate severity of illness, identical symptoms, and no medical complications present during the first days of illness.

Clinical diagnosis of illness was confirmed with the help of laboratory tests and measurements: determination of viral antigens in nasal mucus membrane epithelial cells by immunofluorescence (IF); change in blood serum antibody titers through blood serum complement tests and hemagglutinin inhibition tests, and also by isolation of the virus.

In the hospital studies, all children underwent blood tests and, when necessary, had chest x-rays. In some of the children, biochemical markers were studied, which allowed us to evaluate the status of the liver and exchange processes: C-reactive protein, protein fraction, alanine aminotransferase (ALT), urea, neuraminic and pyrotartaric acid, lactate dehydrogenase and its iso-enzymes. In 45 of the children we studied the effects of

rimantidine, and in 51 children, arbidol, on cell-mediated and humoral immunity markers.

Results and Discussion

Observations showed that in every epidemic season, illness in the vast majority of children began with such symptoms as fever, headache, lethargy, and anorexia. Other symptoms of toxicity (vomiting, vertigo, hemorrhagic and neurological symptoms) occurred in a small percentage of cases. Of the nasopharyngeal inflammatory symptoms, the most common were dry cough and rhinitis. In the case of a mixed infection caused by influenza virus with other AVRI factors, on the first and second days the same clinical symptoms appeared as with the monoinfections, the only difference being that the nasopharyngeal symptoms lasted longer.

Upon evaluation of the efficacy of rimantidine, out of the 554 school-age children studied in the hospital, 88 were determined to have influenza A (H3N2); 117, influenza A (H3N2) combined with other AVRI; 68, influenza A (H1N1); 77, influenza B; 68, influenza groups A and B; 66, groups A and B with other AVRI; and 62, AVRI. All of the 188 children who were polyclinic patients had influenza A (H1N1) (Table 1).

In the drug efficacy evaluation process, one of the most effective indicators was temperature reaction. On the first day of medication, body temperature in most of the children was between 38 and 38.9 degrees Celsius. This was the case in every season of the study, regardless of origin of illness, and was measured with the same frequency in each of the groups. Beginning with the first day of treatment, and in successive days, the frequency of temperature reaction in all children who received rimantidine was statistically much less than in children in control groups (Table 1).

Table 1: Frequency of temperature reaction in children with influenza and other AVRI when given rimantidine treatment

Place of study	Illness	Drug	No. of child-ren	Patients with fever per day after beginning of treatment, %				
				Day 1	Day 2	Day 3	Day 4	Day 5
Hospital	Influenza A	rimantidine	44	45.4	13.6	9.1	2.3	0
	(H3N2)	placebo	44	77.3*	43.2*	27.3*	18.2*	9.1
	Infl. A (H3N2)	rimantidine	50	56.0	30.0	4.0	0	0
	+ other AVRI	placebo	67	80.5*	64.2*	29.8*	12.0	3.0
	Influenza A	rimantidine	42	66.7	28.6	9.5	0	0
	(H1N1)	placebo	34	88.2*	64.7*	35.3*	23.5	5.9
	Influenza B	rimantidine	42	64.3	40.5	14.3	2.3	0
		placebo	35	82.8	68.6*	48.6*	22.8*	8.6
	Infl. A + B	rimantidine	32	68.7	25.0	9.4	0	0
		placebo	36	91.7*	50.0*	33.3*	16.7	5.6
	Infl. A + B	rimantidine	37	48.6	35.1	8.1	0	0
	+ other AVRI	placebo	29	82.7*	65.5*	34.5*	17.2	0
	AVRI (non-	rimantidine	29	51.7	27.6	6.9	3.4	0
	infl. origin)	placebo	33	87.8*	75.7*	54.5*	24.2*	9.1
Polyclinic	Influenza A	rimantidine	98	66.3	38.7	12.2	1.0	0
	(H1N1)	placebo	90	80.2*	65.6*	36.7*	20.0*	4.4

* This wide spread in indicators is reliable in relation to the corresponding experimental group.

In this regard, the most noticeable therapeutic effect was in the groups with influenza type A. In addition, in children with influenza B, the frequency of fever the second day after starting rimantidine was less then in the control group; compared to the control, it was 40.5 to 68.6%, 14.3 to 48.6%, and 2.3 to 22.8% respectively. For children who had influenza A and B, A and B plus other AVRI, or AVRI of non-influenza etiology – as with influenza A, from the second day of treatment a fever reaction was seen much less than in the control groups. This confirms the presence in rimantidine of antioxidant action.

There were differences in the amount of temperature reaction. By the end of the first day of treatment, in the children of all the groups which received rimantidine, body temperature of 38 degrees or higher occurred in 19 – 22% of cases, whereas in the control groups it was 34-58% of cases (p 0.05). Average duration of temperature reaction in the experimental groups was 2.4 – 3.1 days, while in the control it was 3.4 – 3.9 days (p 0.01). Lessening of other symptoms of toxicity also happened earlier in the groups of children who received rimantidine. However, the duration of catarrh (inflammation of nasal and throat passages) was almost the same for both experimental and control groups, and averaged 4.8 – 5.1 days.

The analysis conducted on the efficacy of rimantidine showed a dependence on the time elapse between onset of illness and beginning of treatment. In the polyclinic setting, 55 children received rimantidine on the first day of their illness, and 43 on the second day. Observations showed that the children who received the drug on the first day of illness had fever less frequently than the children in the control group, and also less than the children receiving rimantidine on the second day of illness (Table 2). Early administration of rimantidine also caused other symptoms of toxicity to disappear earlier.

Table 2: Frequency of temperature reaction in children with influenza A (H1N1), depending on when rimantidine treatment was started

Beginning of treatment	Drug	No. of children	Presence of fever per day after beginning of treatment, %					
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
First day of illness	rimantidine	55	100.0	70.8	40.0	14.5	1.8	0
	placebo	45	100.0	93.3*	71.1*	44.5*	31.1*	8.9
Second day of illness	rimantidine	43	100.0	100.0	60.4	37.2	9.3	0
	placebo	45	100.0	100.0	71.1	60.0*	28.9*	8.9

* $p < 0.05$ in relation to this marker in the corresponding experimental group.

The frequency of influenza-related complications was also less in all groups of children receiving rimantidine compared with the control group (1.8 – 5.0% as against 6 – 12.1%, respectively). No side effects were observed in any of the children who had received rimantidine.

Having observed the clinical high level of tolerance and safety of rimantidine in treatment of schoolchildren, we studied its therapeutic effects in a limited group of 60 children aged 3-6 years, who were hospitalized with a clinical diagnosis of influenza in the first or second day of illness. On the basis of generally accepted symptomatic therapy, 28 children received rimantidine in the dose of 1.5 mg/kg body weight three times a day for three days, and 32 received a placebo. The maximum temperature on the first day of illness was the same in the experimental and control groups (38.7 +/- 0.2 C

and 38.8 +/- 0.2 C respectively). Other clinical symptoms between the groups were also equivalent.

At the end of the first day of treatment, fever was noted in 64.3% of children of the experimental group and 87.5% of the control group. In the following days, this indicator was 25.0 and 59.4%, 7.1 and 34.4%, 0 and 21.8%, and 0 and 9.4% respectively. Average duration of temperature reaction was respectively2.5 and 3.8 days ($p < 0.01$). Analogous results proved to exist for other symptoms of toxicity. Neither group showed any complaints associated with taking the drug, any digestive tract problems or allergic reactions.

Hematologic markers did not show any great difference in results for any of the groups in respect of administration of the drug. Biochemical markers after the last day of administration of the drug had a tendency to normalize in every group under study, and in some children actually reached normal levels. These data allow us to conclude that rimantidine has no toxic effects on organ functions in children's bodies.

Upon study of relative and absolute numbers of T-lymphocytes and their subpopulation in the course of illness of 25 children who received rimantidine and 20 children who received only symptomatic treatment, there was seen a lowering of absolute and relative numbers of T-lymphocytes and T-suppressors in the acute illness period of both groups. At around the 7^{th}-8^{th} day of illness, active cell immunity increased in all the children.

In the acute period of illness, there was suppression both of the ability of T-lymphocytes to form blasts, and the presence of PA (phagocytic activity). Stimulation index in the experimental group of children was 14.7 +/- 2.1; in the control group, 13.8 +/- 2.3. In the convalescent period, we noted a positive blastogenesis in both compared groups, with respective numbers of 42.7 +/- 3.3 and 37.8 +/- 4.3. Blood serum tests showed a confirmed growth of viral antibody titers both in the children who received rimantidine, and in the control groups (from 85.7% to 90.8% respectively), which suggests that rimantidine does not have an immunodepressive effect. As further evidence, there is the fact that the numbers of all three classes of serum immunoglobulins (A, M, G) were independent of therapy, and that upon discharge from the hospital these numbers were normal, with no distinction between children who had and had not received rimantidine (Table 3).

Table 3: Serum concentrations of A, M, and G immunoglobulin classes in children, divided by type of treatment they received

Immunoglobulin, g/l		rimantidine (n = 25)	placebo (n = 20)
IgA	A	0.8 +/- 0.09	0.7 +/- 0.1
	B	0.9 +/- 0.07	0.8 +/- 0.09
IgM	A	1.06 +/- 0.06	1.09 +/- 0.08
	B	1.12 +/- 0.08	1.1 +/- 0.07
IgG	A	10.8 +/- 1.1	11.1 +/- 1.2
	B	11.6 +/- 0.9	11.2 +/- 1.25

Note: "A" rows are for acute period of illness; "B" is during the convalescent period.

In IF studies of nasal mucous membrane discharge with influenza groups A and B, we discovered differences both in the amount of viral antigens, and in the duration of the discharge (in comparison with the control group). On the first day of the study, the

number of positive results was the same for all children regardless of therapy. On the third day of treatment it was established that the frequency of occurrence of viral antigens for influenza groups A and B had lowered to 31.9 and 32.7% as against 54.8 and 60.5% before the beginning of treatment ($p < 0.001$). In the control group children, the number of positive results stayed at almost the same as its previous level (45.7 – 53.3%). After the end of rimantidine treatment (5^{th} – 7^{th} day of illness), influenza group A viral antigens could not be detected, while group B antigens were determined at 20.8%; among children of the control group, they were detected in 39.3%.

In the evaluation of the effectiveness of arbidol, we studied 90 children aged 1-6 years, and 68 school-aged children (7 – 14 years). The etiology of illness was influenza type A alone, 75 children (47.5%), 46 of whom were in the experimental group and 29 control; influenza A with other AVRI, 58 (36.7%), of whom 28 were in the experimental group; and non-influenza AVRI, 25 (15.8%) – 16 and 9 children respectively.

Our conducted observations revealed a positive dynamic in the course of illness in all children who received arbidol (Table 4). As shown in Table 4, the duration of all clinical symptoms of illness, including laryngo-tracheal stenosis, was measurably less in the children who received arbidol. At the same time, catarrh-like symptoms, especially in the lungs, did not differ appreciably between the groups. We should also note that separating the analysis between the etiologies of illness (influenza, influenza with other AVRI, and non-influenza AVRI) confirmed the positive dynamic in the course of illness of the children who took arbidol.

Table 4: Duration of basic clinical symptoms in children with influenza and other AVRI with arbidol treatment

Clinical symptoms:	Duration of symptoms in studied groups (M +/- m)		
	Experimental (n = 84)	Control (n = 74)	p
Fever	1.8 +/- 0.16	3.4 +/- 0.59	<0.05
Intoxication	1.9 +/- 0.12	3.8 +/- 0.32	<0.05
Cough	4.1 +/- 0.29	5.5 +/- 0.35	<0.05
Catarrh symptoms:			
Post-nasal congestion	3.5 +/- 0.32	4.8 +/- 0.26	<0.05
In the lungs	5.4 +/- 0.35	6.1 +/- 0.30	<0.05
Laryngo-tracheal stenosis	2.2 +/- 0.13	3.5 +/- 0.23	<0.05

As with the rimantidine treatment, the difference between the experimental and control groups was shown in the rate of high temperature, with the clearest difference when arbidol was given in the first or second day of illness. Determination of arbidol's effect ($p < 0.05$) on the frequency of in-hospital infection (27.1% of children on arbidol vs. 52.1% in the control group) confirmed not only its treatment, but also its prophylactic efficacy. The frequency of illness complications and the duration of the general illness period were both measurably lower in children who received arbidol.

No side effects of any kind appeared with administration of arbidol; the children took it without problem. There also were not noted any substantive differences in hematologic or biochemical indicators in the children receiving the therapy, which shows arbidol does not have any toxic effects on body systems.

To confirm that arbidol's effectiveness in treatment is due not only to viral inhibition, but also to immuno-stimulating properties, we have conducted immunological

tests. These tests showed that although markers for cell immunity were decreased in all the children at onset of illness, after treatment, a greater tendency toward normalization appeared in those children who had received arbidol. It was also established that in the arbidol group, there was a measurable improvement ($p < 0.05$) of T-lymphocytes, particularly killer-T's, in comparison with the control group (57.1% vs. 33.3%). In addition, the studied drug was shown to have an effect on the phagocytic activity of macrophages (Table 5).

Table 5: Arbidol's effects on phagocytic activity of macrophages in sick children

Drug		Ma – index	Ma – number
Arbidol	A	3.0 +/- 1.1	3.1 +/- 1.2
(n = 25)	B	5.9 +/- 1.7*	7.3 +/- 1.5*
Control	A	3.2 +/- 0.9	4.4 +/- 1.1
(n = 22)	B	3.3 +/- 1.0	4.1 +/- 1.3

Note: * $p < 0.05$; "A" rows are for before treatment, and "B" rows, after treatment.

According to the given IF studies on nasal mucous membrane smears, the administration of arbidol facilitated the shortening of the period when viral antigens could be detected.

Thus, on the basis of clinical laboratory studies we have determined the manifest therapeutic efficacy of rimantidine and arbidol in school-aged and younger children, both against influenza caused by various viral serotypes, and against combinations of influenza and other AVRI and against non-influenza AVRI. Administration of the drugs facilitated a decrease in fever reactions and in the development of complications. They also shortened the duration of fever, of other symptoms of toxicity and the illness as a whole. The selected doses of the medications helped shorten the period of isolation of viral antigens in nasal mucous membranes. They did not produce any toxic effects in the body systems of pediatric patients, and arbidol actually had an immuno-stimulating effect on the T-cell network. There were no signs of any inhibitory effects on humoral immunity markers, on the production of antiviral antibodies or their level in the blood.

All of the above allow us to recommend the approval of the chemical preparations for wide use in the sphere of medical treatment against influenza and AVRI in children.

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